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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE TO THE BOARD OF PATENT APPEALS AND INTERFERENCES

Appl. No.	: 09/308,223
Applicant	: Georg KALLMEYER et al.
Filed	: August 12, 1999
Title:	: STABLE LYOPHILIZED PHARMACEUTICAL SUBSTANCES FROM MONOCLONAL OR POLYCLONAL ANTIBODIES
TC/A.U.	: 1642
Examiner	: Brandon J. Fetterolf
Docket No.	: 2924-139
Customer No.	: 6449
Confirmation No.	: 5876

Commissioner for Patents
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August 16, 2006

CORRECTED BRIEF ON APPEAL UNDER 37 C.F.R. §41.37

Sir:

The following comprises the Applicant's Brief on Appeal from the Office Action dated November 1, 2005, in which claims 13, 15-18 and 22-36, were finally rejected. A Notice of Appeal was filed April 28, 2006 along with a Pre-Appeal Brief Request for Review and a petition for a three-month extension of time. A decision on the Pre-Appeal Brief Request was mailed on May 24, 2006 stating that at least one issue remains for appeal. This Appeal Brief is accompanied by the required Appeal fee set forth in 37 C.F.R. § 41.20(b)(2), along with a petition for an extension of time, and is being timely filed.

I.

REAL PARTY IN INTEREST

The owner of the above-referenced patent application and the real party in interest in this appeal is Roche Diagnostics GmbH, Federal Republic of Germany.

II.

RELATED APPEALS AND INTERFERENCES

The Applicant is unaware of any other appeals or interferences related to the subject matter of this appeal.

III.

STATUS OF CLAIMS

Claims 13, 15-18 and 22-36 are pending in the application. Claims 13, 15-18 and 22-36 were rejected in the Final Office Action dated November 1, 2005. Claims 1-12, 14, and 19-21 have been canceled. Applicant appeals from the rejection of claims 13, 15-18 and 22-36. The appealed claims are reproduced in the Appendix attached hereto.

IV.

STATUS OF AMENDMENTS

No Amendments have been submitted since the final rejection dated November 1, 2005.

V.

SUMMARY OF THE CLAIMED SUBJECT MATTER

The present invention is directed to lyophilized pharmaceutical preparations of monoclonal or polyclonal antibodies. Monoclonal and polyclonal antibodies are increasingly important for therapeutic and diagnostic purposes and methods for the stabilization of lyophilized antibodies are known in the art (Specification page 2, line 18 to page 5, line 26). However, the known methods for stabilization of antibodies often require stabilizers which are not acceptable from a medical point of view (Specification page 5, line 27 to page 6, line 22). Polymers (such as polyethylene glycol and gelatin) and proteins (such as serum albumin) pose a risk due to their origin (e.g. viral contamination) and can cause an allergic reaction (Specification page 5, line 30 to page 6, line 4).

The present inventors have surprisingly found that stable pharmaceutical lyophilisates of monoclonal or polyclonal antibodies are obtained when the preparation contains the antibody, an amino sugar, at least one amino acid, and a surfactant (Specification page 7, lines 3-9). These preparations according to the present invention are physiologically well tolerated, have a relatively simple composition and can be dosed exactly (Specification page 7, lines 12-14). The preparations exhibit no detectable degradation products when subjected to multiple freezing and thawing cycles or during long term storage (Specification page 7, lines 14-17). The claimed preparations exhibit no particle formation (i.e. turbidity) after reconstitution with water (Specification page 8, lines 10-13). Further embodiments and features of the present

invention are listed in the following paragraphs, which provide a detailed description of the claimed features of the present invention.

As recited in independent claim 13, one aspect of the invention is embodied in a lyophilized preparation containing a monoclonal antibody or polyclonal antibody, an amino sugar, at least one amino acid; and a surfactant, but does not contain polyethylene glycols or additional proteins (Specification page 7, lines 3-9).

As recited in independent claim 27, another aspect of the invention is embodied in a preparation where the lyophilizate consists essentially of a monoclonal antibody or polyclonal antibody, an amino sugar, at least one amino acid, a surfactant, and an inorganic acid as a buffering agent, but does not contain polyethylene glycols or additional proteins (Specification page 13, line 13 to page 14, line 15).

As recited in independent claim 36, the invention is further embodied in a method for preparing a lyophilizate by mixing a buffered solution containing a monoclonal antibody or a polyclonal antibody, an amino acid sugar, at least one amino acid and a surfactant, wherein the mixed solution was a pH value of 5-8; and lyophilizing the mixed solution, wherein the lyophilizate contains no polyethylene glycols or additional proteins (Specification page 14, line 30 to page 15, line 10).

VI.

GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

The only issue on appeal is whether claims 13, 15-18 and 22-36 are unpatentable under 35 U.S.C. § 103(a) as obvious over Andya in view of Michaelis.

VII.

ARGUMENT

Claims 13, 15-18 and 22-36 are not obvious over Andya in view of Michaelis because they recite subject matter not shown or suggested by Andya in view of Michaelis.

Andya in view of Michaelis fails to render obvious any of claims 13, 15-18 and 22-36. Claims 13, 15-18 and 22-36 are directed to a lyophilizate which contains a monoclonal or polyclonal antibody, an amino sugar, at least one amino acid, and a surfactant, where the lyophilizate does not contain polyethylene glycols or additional proteins; a composition containing the lyophilizate and a method for preparing the lyophilizate. The office actions contend that one skilled in the art would be motivated to combine Andya and Michaelis to arrive at the present invention because both of these references teach the preparation of stable pharmaceutical compositions. Applicants respectfully point out that Michaelis discloses the addition of an amino sugar to stabilize a protein which is a member of the four-helix bundle class of cytokines (G-CSF) not antibodies while Andya is directed to antibody preparations which do not contain amino sugars. Antibodies and cytokines are in different protein classes and have different structures and therefore different stabilization requirements.

The Office Action of November 1, 2005 states that it would have been obvious to modify the lyophilizate of Andya to include an amino sugar as taught by Michaelis. Michaelis discloses the addition of an amino sugar to stabilize G-CSF protein not antibodies. Applicants respectfully point out that it is known that different protein

classes required different stabilizers, not all stabilizers are suitable for all proteins. Osterberg (WO 94/07510) states on page 4, lines 25-32 that:

"Proteins are different with regard to physico-chemical properties. When preparing a pharmaceutical preparation which should be physico-chemical acceptable, and stable for a long time, consideration cannot only be taken to the physiological properties of the protein but also other aspects must be considered such as the industrial manufacture, easy handling for the patient and safety for the patient. **The results of these aspects are not predictable when testing different formulations and there often is a unique solution for each protein**," (emphasis added).

Osterberg points out that different proteins are different in their physico-chemical properties and thus for each protein or class of proteins an individual solution has to be developed and thus it cannot be predicted that the same formulation will be useful for a different class of protein.

Manning (Pharmaceutical Research, Vol. 6, No. 11, 1989, p. 903-918) is a general article related to the stability of proteinaceous pharmaceuticals. On page 913, left column, first sentence of the last paragraph, it is stated that "protein stability encompasses many complicated and interrelated chemical and physical processes". From this it can be concluded that for every protein or class of proteins an individual solution has to be found due to different physical and chemical constraints. Thus, one skilled in the art would not extrapolate the disclosure in Michaelis to any and all protein classes and certainly not to any and all pharmaceutical compositions as suggested in the office actions.

Osterberg's and Manning's conclusions are supported by the fact that different substances are indicated as good stabilizers in some references and as not useful as a stabilizer in other references. For example, Kunihiro (EP 0 689 843) page 4, line 4 - 7, indicates that the combination of soluble thrombomodulin together with albumin, purified gelatin, glycine, glucose or mannitol **failed** to exhibit sufficient long term stability. Thus, this document contradicts the contention in the office actions that Michaelis' teaching can be applied to any and all pharmaceutical preparations. Kunihiro teaches away from the current invention in that the combination of an amino acid with a sugar had no beneficial effect on stability.

Hanson (chapter 7 in Stability of Protein Pharmaceuticals, 1992) indicates on page 217, second paragraph, line 6 to 7 that "Ornithine, aspartic acid, glutamic acid, alanine and glycine did not stabilize" intravenous immunoglobulin preparations. Thus, Hanson also contradicts the contention in the office action that Michaelis' teaching can be applied to any and all pharmaceutical preparations and teaches away from the current invention which shows that the use of the amino acids listed in Hanson improve the stability of the lyophilized antibody formulation.

Metzner (EP 0 733 702) which is equivalent to US Patent No. 6,204,036 indicates that histidine and glutamic acid alone, even without further additives, show sufficient stabilization (page 3, line 9, of the German text, column 5, lines 56-58 of the US text). In contrast to Metzner, Michaelis (WO 94/14465) states on page 10, lines 4 to 7 of the German WO 94/14465 that the addition of glutamic acid has no significant impact on the storage stability. Both Metzner and Michaelis also indicate that the

surfactant had no impact on storage stability (Metzner page 3, lines 42-43 or col. 6, lines 48-50 in the U.S. Patent, Michaelis page 9, last paragraph of WO 94/14465) but the present inventors have found that the surfactant does affect stability in the present invention. Thus, prior art formulations for stabilizing different pharmaceutical preparations clearly cannot be generalized.

Nema (J. Parent Sci. Technol., 47, p. 76-83, 1993) states on page 81, left column, last sentence of the first paragraph: "A surprising result was obtained with trehalose, a disaccharide which is considered by many workers to be one of the best cryoprotectants, but proved to be ineffective in this study at a concentration of 5%w/v". This statement also supports the conclusion of the non-transferability of formulations to different classes of proteins.

In view of the above discussed references, three conclusions can be drawn.

1) There is no suggestion that combining different compounds discussed in different references will result in a formulation with further improved stability. Furthermore there is no suggestion in these documents as to the particular combination of compounds as described in the current invention.

2) As can be seen from these references, it is not possible to generally transfer the known composition of a formulation useful with one class of proteins or with one protein to other proteins. It was not probable or predictable that a formulation for stabilizing a cytokine would be successful with the antibody preparation of the present invention.

3) There are no cited documents that suggest or disclose that a formulation for stabilizing a non-antibody protein can be used for the stabilization of a lyophilized antibody preparation.

Applicants also point out that Andya teaches at column 29, lines 49-50, that "reducing sugars are not suitable as lyoprotectants for the antibody". In contrast to this, the present inventors have found that amino sugars derived from reducing sugars such as glucose or galactose are suitable for use in the present invention.

Applicants contend that one skilled in the art would not expect Michaelis' formulation to be useful for any and all pharmaceutical preparations as different protein classes require different stabilization agents and there is no reason to believe that Michaelis' formulation would stabilize antibody preparations such as Andya's antibody formulation.

Conclusion

For all of the above noted reasons, it is strongly contended that certain clear differences exist between the present invention as claimed in claims 13, 15-18 and 22-36 and the prior art relied upon by the Examiner. It is further contended that these differences are more than sufficient evidence that the present invention would not have been obvious to a person having ordinary skill in the art at the time the invention was made.

This final rejection being in error, therefore, it is respectfully requested that this honorable Board of Patent Appeals and Interferences reverse the Examiner's decision in this case and indicate the allowability of application claims 13, 15-18 and 22-36.

In the event that this paper is not being timely filed, the applicant respectfully petitions for an appropriate extension of time. Please charge any fee or credit any overpayment pursuant to 37 §C.F.R. 1.16 or §1.17 to Deposit Account No. 02-2135.

Respectfully submitted,

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VIII.

APPENDIX OF CLAIMS ON APPEAL

Claims 1-12 (Cancelled).

13. A lyophilizate, comprising

(a) a monoclonal antibody or a polyclonal antibody;

(b) an amino sugar;

(c) at least one amino acid; and

(d) a surfactant,

wherein the lyophilzate contains no poly ethylene glycols or additional proteins.

14. (Cancelled).

15. The lyophilizate of claim 13, wherein the lyophilizate contains a single amino acid or two different amino acids.

16. The lyophilizate of claim 13, further comprising a buffering agent or an isotonizing agent which is present in an amount such that a reconstituted solution of the lyophilizate has a pH value of 5-8.

17. The lyophilizate of claim 13, wherein the lyophilizate is storage-stable for a time period of at least three months at a temperature of about 4-12°C.

18. The lyophilizate of claim 13, wherein the lyophilizate is storage-stable for a time period of at least three months at a temperature of about 18-23°C.

Claims 19-21 (Canceled).

22. The lyophilizate of claim 13, wherein the amino sugar comprises at least one member selected from the group consisting of glucosamine, N-methyl-glucosamine, galactosamine and neuraminic acid.

23. The lyophilizate of claim 13, wherein the amino acid comprises at least one member selected from the group consisting of arginine, lysine, histidine, ornithine, glutamic acid, aspartic acid, isoleucine, leucine, alanine, phenylalanine, tyrosine and tryptophan.

24. The lyophilizate of claim 13, wherein the surfactant comprises a polysorbate or a polyoxyethylene-polyoxypropylene polymer.

25. The lyophilizate of claim 13, wherein the monoclonal antibody or the polyclonal antibody has a molecular weight of 50-200 kDa per monomer unit.

26. The lyophilizate of claim 13, wherein the monoclonal antibody or the polyclonal antibody is directed against an antigen selected from the group consisting of hepatitis B virus, AIDS virus, cytomegalovirus, meningoencephalitis virus, rubella virus, measles virus, rabies pathogen, Pseudomonas aeruginosa, varicella-zoster virus, tetanus pathogen, van Willebrandt factor, nerve growth factor receptor, platelet derived growth factor receptor, selectin, integrin and diphtheria pathogen.

27. A lyophilizate, consisting essentially of

(a) a monoclonal antibody or a polyclonal antibody;

(b) an amino sugar;

(c) at least one amino sugar;

(d) a surfactant; and

(e) an inorganic acid as a buffering agent,

wherein the lyophilzate contains no poly ethylene glycols or additional proteins.

28. A liquid pharmaceutical composition comprising the lyophilizate of claim 13 dissolved in a physiologically acceptable solution.

29. The liquid pharmaceutical composition of claim 28, wherein the composition has a pH value of 5-8.

30. The liquid pharmaceutical composition of claim 28, wherein the composition contains 1-10 mg/ml of antibody.

31. The liquid pharmaceutical composition of claim 28, wherein the composition contains up to 200 mg/ml of sugar or amino sugar.

32. The liquid pharmaceutical composition of claim 28, wherein the composition contains up to 100 mg/ml of amino acid.

33. The liquid pharmaceutical composition of claim 28, wherein the composition contains 0.05-0.5 mg/ml of surfactant.

34. A liquid pharmaceutical composition comprising the lyophilizate of claim 27 dissolved in a physiologically acceptable solution.

35. The liquid pharmaceutical composition of claim 30, wherein the composition has a pH value of 5-8.

36. A method of preparing a lyophilizate, the method comprising mixing a buffered solution containing a monoclonal antibody or a polyclonal antibody, an amino acid sugar, at least one amino acid and a surfactant, to prepare a mixed solution, wherein the mixed solution was a pH value of 5-8; and

lyophilizing the mixed solution, wherein the lyophilizate contains no polyethylene glycols or additional proteins.

IX.

EVIDENCE APPENDIX

A copy of the background references discussed above and in applicant's January 31, 2006 response were attached in the Appeal Brief filed July 28, 2006. These references were submitted with the information disclosure statement filed on September 2, 2005.

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RELATED PROCEEDINGS APPENDIX

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